PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PTO1

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/002011	20.05.2005	20.05.2004

International Patent Classification (IPC) or both national classification and IPC
B01J13/02, A01N25/28, A01N35/06, A01N35/02, A01N31/16, A01N31/08, A01N31/02, A61K9/50

Applicant
EDEN RESEARCH PLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 79-81

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 79-81

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	15-24,33,35,38,56,57,64-78,83,84
	No:	Claims	1-14,25-32,34,36,37,39-55,58-63,82
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-78,82-84
Industrial applicability (IA)	Yes:	Claims	1-78,82-84
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: WO 2005/070213 A (EDEN RESEARCH PLC; FRANKLIN, LANNY; OSTROFF, GARY) 4 August 2005 (2005-08-04)
D2: EP-A-0 242 135 (AD2 LIMITED; AD2 LTD) 21 October 1987 (1987-10-21)
D3: WO 96/36433 A (CPC INTERNATIONAL INC; HOBSON, JOHN, CHARLES; GREENSHIELDS, RODERICK,) 21 November 1996 (1996-11-21)
D4: GB-A-2 162 147 (DUNLOP LIMITED) 29 January 1986 (1986-01-29)
D5: WO 03/020024 A (XIMED GROUP PLC; FRANKLIN, LANNY, U) 13 March 2003 (2003-03-13)
D6: WO 00/49865 A (THE VAN KAMPEN GROUP, INC) 31 August 2000 (2000-08-31)
D7: WO 03/070286 A (XIMED GROUP PLC) 28 August 2003 (2003-08-28)
D8: WO 03/069993 A (PHARMESSEN SCIENTIFIC, INC) 28 August 2003 (2003-08-28)

2) The present application relates to compositions comprising a **hollow glucan particle** or a **cell wall particle** encapsulating a **terpene component**. It further relates to the preparation of such compositions and to their use in preventing and treating infections in plants and animals.

3) Re Item III

According to Rule 34.1(iv) PCT, no search has not been carried out for the methods of treatment by therapy defined in claims 79-81. Therefore, the subject-matter of claims 79-81 is not the object of the present written opinion, which is based only on the compositions, methods, and uses of claims 1-78 and 82-84.

4) Re Item V

4.1 Novelty (Art. 33(2) PCT)

Regarding Claim 82, the Applicant's attention is drawn to the fact that the mention of the intended use (prevention or treatment of an infection **in a plant**) in composition claims is considered as merely descriptive and is not to be considered as a technical limiting feature

(see PCT-ISPE-Guideline 12.05). Thus, composition Claim 82 encompasses any composition for any use, that contains a hollow glucan particle encapsulating a terpene and which is suitable for treating a plant.

D2 discloses (cf. abstract) a method of producing an encapsulated material into the cell wall of a microorganism such as a fungus, a bacterium, or an alga. The microbe is contacted with an encapsulatable material in liquid form, being capable of diffusing into the microbial cell across its wall. The microbe is preferably a fungus such as *Saccharomyces cerevisiae* (baker's yeast), *Kluyveromyces fragilis* (dairy yeast), *Candida utilis*, or *Aspergillus niger* (cf. pg. 2, l. 28-40). Examples of materials which may be encapsulated are benzaldehyde, essential oils, pheromones, insecticides, dyes, vitamins, drugs, detergents, rodenticides, nematocides, insect-repellants, herbicides, fungicides, molluscicides, insect- and plant-growth regulators, food colorants, and wintergreen oil (cf. pg. 3, l. 5-13). The microbe may be pretreated at an elevated temperature and/or with a chemical (e.g. sodium hydroxide) to enhance permeability prior to encapsulation (cf. pg. 3, l. 27-33). The microbial capsules of **D1** remain stable for a considerable period of time (at least 1 year) and may contain up to 75% of encapsulated material based on the total weight of the particle (cf. pg. 3, l. 39-49). Thus, insecticides encapsulated by this method are usually more stable and may be more attractive to insects than are non-encapsulated insecticides (cf. pg. 4, l. 7-8). The microcapsules may be separated from the treatment medium by centrifuging, freeze-drying, or spraying-drying (cf. pg. 3, l. 50-52). In the examples, several substances containing terpenes have been encapsulated into commercially available yeasts: lavender oil, clove oil, cedar oil, mint oil, peppermint oil, eucalyptus oil, menthol crystals, onion extract, mustard oil, lemon fragrance, apple blossom fragrance, and garlic oil. In other examples the insecticides malathion and diazinon or the biocide dichorophen have also been encapsulated. Thus, the disclosure of **D1** anticipates the subject-matter of claims 1-6, 9-14, 25-30, 36, 37, 39-55, 58-60, 62, 63, and 82.

D3 relates equally (cf. abstract) to an encapsulated product comprising a shell of microbial cell wall-derived material, such as *Saccharomyces cerevisiae*, and a substance encapsulated within the shell. In this document, the microbial shell is dyed to give a colour which is visible in the bulk product. The method of encapsulation and the substances which may be encapsulated are as mentioned in document **D2** (cf. **D3**: pg. 4, l, 22-27 and pg. 3, l. 7-31). Examples 1-10 show the encapsulation of lemon or peppermint oil into baker's yeast cell

walls. In Example 15, encapsulated lemon oil was incorporated into a standard commercially available mayonnaise-type dressing. **D3** is regarded as relevant for the novelty of the subject-matter of claims 1-14, 25-32, 34, 39-55, 59-63, and 82.

Summarizing, the subject-matter of claims 1-14, 25-32, 34, 36, 37, 39-55, 58-63, and 82 may not be regarded as novel; Novelty may be acknowledged only for claims 15-24, 33, 35, 38, 56, 57, 64-78, 83, and 84.

4.2 Inventive Step (Art. 33(3) PCT)

The subject-matter for which novelty cannot be acknowledged may neither be regarded as inventive. Accordingly, the following examination in terms of inventive step has been restricted to the subject-matter of claims 15-24, 33, 35, 38, 56, 57, 65-78, 83, and 84.

The document **D5** discloses (cf. abstract; pg. 12, l. 26-17; pg. 14, l. 19-28; and examples) compositions and methods for prevention and treatment of plant infections. The compositions comprise a single terpene, a terpene mixture, or a liposome-terpene(s) composition. They may be a solution of the terpene in a carrier such as water as well as a suspension or an emulsion of the terpene in the carrier (water) by means of a surfactant. The compositions may be administered before of after the onset of the disease and are effective against bacteria, mycoplasmas, phytoplasmas, or fungi. Preferred terpenes and surfactants are cited on pg. 14, l. 19-28 and pg. 13, l. 1-13. In the examples, the effectiveness of solutions, suspensions or liposomes containing citral or mixtures β-ionone/L-carvone/citral have been tested against plant pests.

Similar compositions to those of **D5** have been disclosed in **D6**, **D7**, and **D8** (cf. abstracts) as herbicides, bactericides and/or fungicides for the protection or treatment of plants (**D6**), for the disinfection of surfaces or the indoor air (**D7**), or for the therapeutic treatment of a patient suffering from bacterial, fungal, or protozoal infections (**D8**).

Documents **D5-D8** are considered to represent the closest state of the art.

D4 relates (cf. abstract) to an encapsulated product comprising a microbial capsule having a lipid content of less than 10% by weight and containing a substantial quantity of an organic

liquid. An advantageous embodiment of **D4** (cf. pg. 2, l. 99-105) is the production of encapsulated insecticides. Such encapsulated insecticides, especially those encapsulated by yeasts, often are found to be more stable and more attractive to insects than non-encapsulated insecticides or insecticides encapsulated in synthetic substances. Encapsulated insecticides are illustrated in the examples X-XVI.

The subject-matter of the application which may be regarded as novel differs from the closest prior art in the fact that the biocidal terpene composition is in the form of a terpene component encapsulated within a cell wall particle. This particular formulation is suggested by **D2** and **D4** for biologically active compounds having the same activity, as providing a higher stability compared to usual emulsions and suspensions or to ingredients encapsulated in synthetic materials. The skilled person confronted with the problem of preparing terpene formulations having a higher stability would thus, in the light of the documents **D5** to **D8** in combination with **D2** or **D4**, arrive at compositions, methods, and uses as presently claimed. The subject-matter of the instant application may thus not be regarded as inventive in the sense of Art. 33(3) PCT.

4.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-78 and 82-84 (see also point 3 above).

5) Re Item VI

The document **D1** has been published after the filing date (20.05.2005) of the present application and therefore, it is not regarded as prior art according to Rule 64.1(b)(ii) PCT. However, this document could be considered as relevant prior art within the European examination procedure for the assessment of novelty, according to Article 54(3) EPC, since **D1** claims the earlier priority of 23.01.2004.

6) Re Item VII

The documents cited in the description do not appear to be essential to the performance of the invention as required by Article 5 PCT. Thus, the sentence on pg. 7, l. 23-25 that "*the teachings of the abovementioned patents and applications are incorporated herein by*

reference" should be deleted (see PCT Guidelines ISPE 4.26).

The reference to the co-pending application US60/538,627 on pg. 26, l. 10 should be replaced by a reference to the corresponding document which has been made available to the public (Art. 5 PCT).

7) Re Item VIII

The registered trademarks in Claim 24 have no precise meaning as they are not internationally accepted as descriptive terms, thereby rendering the definition of the these claims unclear (Art. 6 PCT).

The relative terms "about" or "approximately" in claims 26, 42-45, 57 and 60 have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Art. 6 PCT).

Claims 27-29 are not clearly defined (Art. 6 PCT). The claims attempt to define the subject-matter in terms of the result to be achieved (killing bacteria, fungi, mold, or mycoplasma), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. This also applies to Claim 52, which discloses a method of encapsulation wherein step c) defines the conditions for incubating the terpene component with the glucan or cell wall particle as "suitable conditions for terpene encapsulation", without precising the actual conditions needed.

Claim 25 is inconsistent (Art. 6 PCT) since it is impossible to have a composition containing 99% by volume surfactant and the given minimum volumes of particles and terpenes. The same applies for Claim 26, wherein a composition comprising 90% w/w particles may not contain 10% w/w terpenes and 0.1% w/w surfactant.

In Claim 50, the word "parental" should read "parenteral".